

## Medical Genetics Summaries on the NCBI Bookshelf: a pharmacogenomics resource for clinicians

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04/26/2017



## Medical Genetics Summaries on the NCBI Bookshelf: a pharmacogenomics resource for clinicians

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Each chapter describes information about a drug,  
known impacts of genetic variation on drug  
response (eg. efficacy, toxicity, side effects) and  
actionable information (eg. relevant genetic  
testing, how to interpret test results to optimize  
therapy)

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## Medical Genetics Summaries (MGS)

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**Concise reviews about genetic variation and  
drug responses, accessible at the point of  
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- Created by NCBI
- Peer reviewed
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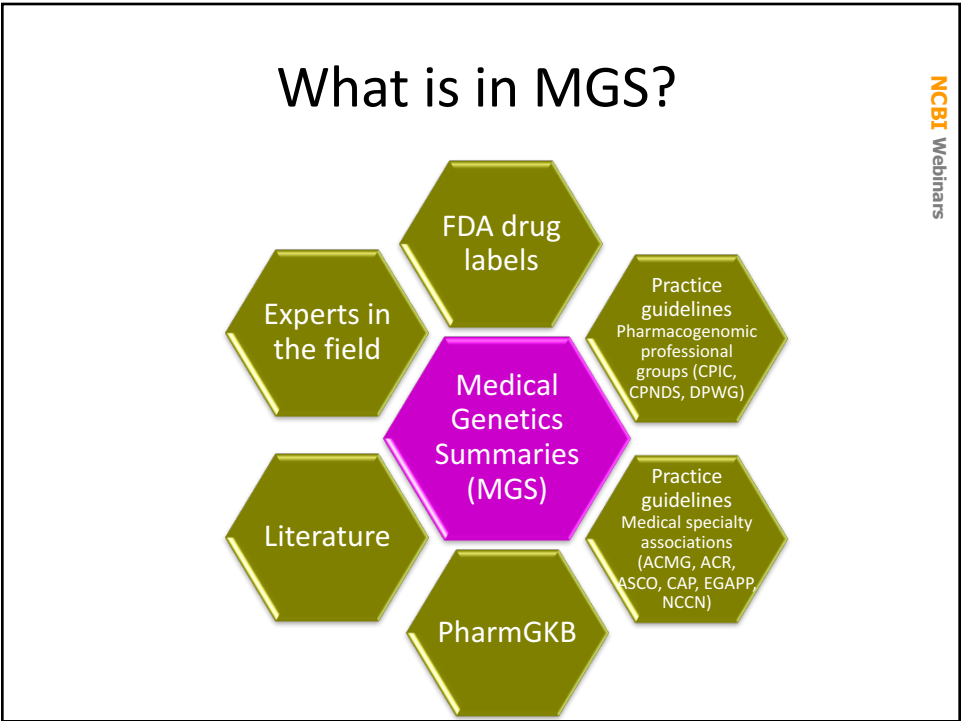
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**Abacavir Therapy and *HLA-B\*57:01* Genotype**  
Laura Dean.  
Created: September 1, 2015.

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[Amitriptyline Therapy and *CYP2D6* and *CYP2C19* Genotype]  
Laura Dean.  
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[Aripiprazole Therapy and *CYP2D6* Genotype]  
Laura Dean.  
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[Atomoxetine Therapy and *CYP2D6* Genotype]



# How to access the MGS

## GTR - database of orderable clinical and research genetic tests:

[www.ncbi.nlm.nih.gov/gtr/](http://www.ncbi.nlm.nih.gov/gtr/)

## MedGen - portal to information about phenotypes with a genetic component:

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GTR: GENETIC TESTING REGISTRY

Advanced search for tests

Conditions/Phenotypes

Search

GTR Home > Conditions/Phenotypes > Venlafaxine response

Venlafaxine response

Synonyms:

Effector response

Modes of inheritance:

Summary

Venlafaxine is an antidepressant used in the treatment of major depressive disorder, anxiety, and panic disorders. Venlafaxine belongs to the drug class of serotonin and norepinephrine reuptake inhibitors (SNRI). The CYP2D6 enzyme metabolizes a quarter of all prescribed drugs, including venlafaxine. This enzyme converts venlafaxine to the active metabolite, O-desmethylvenlafaxine (ODV). Individuals who carry two inactive copies of CYP2D6 ("poor metabolizers") may have decreased capacity to metabolize venlafaxine, resulting in less active metabolite in their system. In contrast, individuals who carry more than two copies of functional CYP2D6 alleles ("ultra-rapid metabolizers") may have an enhanced capacity to metabolize venlafaxine, resulting in more increased active metabolite in their system. The FDA states that because the total exposure of venlafaxine and ODV is similar in poor and extensive (normal) metabolizers, there is no need for different venlafaxine dosing regimens for these individuals. However, the Dutch Pharmacogenetics Working Group recommends that both poor and intermediate metabolizer genotypes should be treated with an alternative drug, or lower doses of venlafaxine based on clinical response and drug levels. For ultra-rapid metabolizer genotypes, they recommend that either the dose of venlafaxine be increased up to 150% of the normal dose, or an alternative drug used. [from Medical Genetics Summaries #]

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Tramadol response

MedGen UID: 452495 - Concept ID: C0678023 - Sign or Symptom

Synonyms:

Ultram response

Drug:

Tramadol

Gene (location): CYP2D6 (22q13.2)

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Definition

Tramadol is an analgesic used to treat moderate to moderately severe pain. It is a synthetic opioid, related to codeine, and is used to treat both acute and chronic pain. Tramadol is often prescribed for post-operative pain, and pain caused by cancer, osteoarthritis, and other musculoskeletal diseases. The CYP2D6 enzyme metabolizes a quarter of all prescribed drugs, including tramadol. Individuals who carry two inactive copies of CYP2D6 are known as poor metabolizers and have higher plasma concentrations of tramadol compared with individuals who have two copies of normal activity alleles. Individuals who carry one or more reduced or inactive copies of CYP2D6 are known as intermediate metabolizers, and individuals who carry more than two active copies of CYP2D6 are known as ultra-rapid metabolizers. The FDA states that the levels of tramadol are approximately 20% higher in poor metabolizers compared to extensive ("normal") metabolizers, while concentrations of the tramadol metabolite, M1, are 40% lower. Inhibitors of CYP2D6, such as fluoxetine and antipyrine, also inhibit the metabolism of tramadol, and the full pharmacological impact of these alterations of tramadol dose is unknown. A guideline from the Dutch Pharmacogenetics Working Group includes dose recommendations for poor metabolizers (either select an alternative drug—not oxycodone or codeine—or be alert to the symptoms of insufficient pain relief). It also contains dose recommendations for intermediate metabolizers (be alert to decreased efficacy of tramadol, consider increasing the dose and if the response is still inadequate, either select an alternative drug—not oxycodone or codeine, or be alert to the symptoms of insufficient pain relief) and ultra-rapid metabolizers (either reduce the dose of tramadol by 30% and be alert to adverse drug events, or select an alternative drug (e.g., acetaminophen, NSAID, morphine—not oxycodone or codeine). [from Medical Genetics Summaries]

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- Pertuzumab Therapy and *ERBB2 (HER2)* Genotype
- Phenytoin Therapy and *HLA-B\*15:02* and *CYP2C9* Genotypes
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### Codeine Therapy and CYP2D6 Genotype

Laura Dean, MD.

NCBI  
dean@ncbi.nlm.nih.gov

Created: September 20, 2012; Last Update: March 8, 2016.




Codeine is used to relieve mild to moderately severe pain, and it belongs to the drug class of opioid analgesics.

The hepatic CYP2D6 enzyme metabolizes a quarter of all prescribed drugs, including codeine. CYP2D6 converts codeine in to its active metabolite, morphine, which provides its analgesic effect. However, pain relief may be inadequate in individuals who carry two inactive copies of *CYP2D6* ("poor metabolizers"), because of reduced morphine levels.

In contrast, individuals who carry more than two functional copies of the *CYP2D6* gene ("ultrarapid metabolizers") are able to metabolize codeine to morphine more rapidly and more completely. As a result, even with normal doses of codeine, these individuals may experience the symptoms of morphine overdose, which include extreme sleepiness, confusion, and shallow breathing. Nursing mothers may also produce breast milk containing higher than expected levels of morphine that can lead to severe adverse events in their infants (1).

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Genetic testing is available for many (~30) of the variant *CYP2D6* alleles. Usually a patient's result is reported as a diplotype, which includes one maternal and one paternal allele, e.g., *CYP2D6* \*1/\*2. When patients have more than two copies of the *CYP2D6*, the copies of the allele are denoted by an "xN", e.g., *CYP2D6*\*2x2.

If the test results include an interpretation of the patient's predicted metabolizer phenotype, this should be confirmed by checking the diplotype and calculating the CYP2D6 activity score. Each allele is assigned an activity value: 0 for nonfunctional, 0.5 for decreased function, and 1 for each copy of a normal function allele. The total CYP2D6 activity score is the sum of the values assigned to each allele—patients with a score of 1.0, 1.5, or 2.0 represent a range of extensive metabolizers with normal enzyme activity. Poor metabolizers have an activity score of 0, patients with a score of 0.5 are intermediate metabolizers, and patients with a score of greater than 2.0 are ultrarapid metabolizers (see [Table 1](#)) (2).

Variants in other genes, such as *COMT*, *ABCB1*, *UGT2B7* and *OPRM1*, may also influence an individual's response to codeine. However, evidence is lacking on whether genetic testing for these variants will aid optimum codeine dosing ([6, 26-28](#)).

# Genetic test report

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Pharmacogenetics 

**CODEINE**

Gene Tested - CYP2D6

Description

STANDARD DOSING

ULTRARAPID METABOLIZER

EXTENSIVE METABOLIZER

INTERMEDIATE METABOLIZER


POOR METABOLIZER

This patient's genotype is associated with normal CYP2D6 enzyme activity, typical systemic exposure to codeine's active metabolite, morphine, and a typical response to standard doses of codeine. Exercise caution when codeine is administered to a breastfeeding mother, and inform her about the risk for opioid overdose. Only use the lowest effective dose, and carefully monitor the mother-infant pair for signs of opioid toxicity.


CODEINE

Genetic Result: CYP2D6 \*1/\*41


GENE/LOCUS	MARKER	GENOTYPE
CYP2D6	rs16947	T/C
CYP2D6	rs769258	G/G
CYP2D6	rs1865852	C/C
CYP2D6	rs1080985	C/C
CYP2D6	rs3802097	G/G
CYP2D6	rs5030655	T/T
CYP2D6	rs5030656	AAG/AAG
CYP2D6	rs5030862	G/G
CYP2D6	rs5030863	C/C




## Allele nomenclature



Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
<i>CYP2D6</i> *4	1846G>A	<a href="#">NM_000106.4:c.506-1G&gt;A</a>	Not applicable - variant occurs in a non-coding region	<a href="#">rs3892097</a>
<i>CYP2D6</i> *5	Not applicable - variant results in a whole gene deletion			
<i>CYP2D6</i> *6	1707 del T Trp152Gly	<a href="#">NM_000106.4:c.454delT</a>	<a href="#">NP_000097.2:p.Trp152Glyfs</a>	<a href="#">rs5030655</a>
<i>CYP2D6</i> *10	100C>T Pro34Ser	<a href="#">NM_000106.4:c.100C&gt;T</a>	<a href="#">NP_000097.2:p.Pro34Ser</a>	<a href="#">rs1065852</a>
<i>CYP2D6</i> *17	Includes*: 1023C>T (Thr107Ile) 2850C>T (Cys296Arg)	<a href="#">NM_000106.4:c.320C&gt;T</a>	<a href="#">NP_000097.2:p.Thr107Ile</a>	<a href="#">rs28371706</a>
		<a href="#">NM_000106.4:c.886T&gt;C</a>	<a href="#">NP_000097.2:p.Cys296Arg</a>	<a href="#">rs16947</a>
<i>CYP2D6</i> *36	Includes: 100C>T (Pro34Ser) 4180G>C	<a href="#">NM_000106.4:c.100C&gt;T</a>	<a href="#">NP_000097.2:p.Pro34Ser</a>	<a href="#">rs1065852</a>
		<a href="#">NM_000106.5:c.1457G&gt;C</a>	<a href="#">NP_001020332.2:p.Ser435Thr</a>	<a href="#">rs1135840</a>
<i>CYP2D6</i> *41	2988G>A	<a href="#">NM_000106.4:c.985+39G&gt;</a>	Not applicable – variant occurs in a non-coding region	<a href="#">rs28371725</a>



## Activity status of relevant alleles



Activity status of selected *CYP2D6* alleles

Allele type	<i>CYP2D6</i> Alleles
Normal function	<span style="border: 2px solid red;">*1</span> , *2, *33, *35
Decreased function	*9, *10, *17, *29, <span style="border: 2px solid red;">*41</span>
No function	*3-*8, *11-*16, *19-*21, *38, *40, *42

For a detailed list of *CYP2D6* alleles, please see ([18](#)).

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# Codeine therapy recommendations based on CYP2D6 phenotype, adapted from CPIC

Phenotype	Activity score	Phenotype details	Genotype	Examples of diplotypes	Recommendations for codeine therapy <sup>1</sup>	Considerations for alternative opioids
Ultrarapid metabolizer (approximately 1–3% of patients)	Greater than 2.0	Increased enzyme activity. Increased formation of morphine following codeine administration, leading to higher blood levels.	More than two copies of normal function alleles	*1/*1xN *1/*2xN	Avoid codeine use due to potential for toxicity.	Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.
Normal metabolizer (approximately 77–92% of patients)	1.0–2.0*	Normal enzyme activity. Normal morphine formation.	Two normal function alleles, or two decreased function alleles, or one normal function allele and one decreased or no function allele, or combinations of duplicated alleles that result in an activity score of 1.0 to 2.0	*1/*1 *1/*2 *2/*2 *1/*41 *1/*4 *2/*5 *1/*10	Use label-recommended age- or weight-specific dosing.	
Poor metabolizer (approximately 5–10% of patients)	0	Low or absent enzyme activity. Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief.	Two no function alleles	*4/*4 *4/*3 *5/*5 *4/*6	Avoid codeine use due to lack of efficacy.	Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.

\* Activity scores are based on the formation of morphine from codeine. Other investigators may define normal metabolizers with a score of 1.5–2.0, and intermediate metabolizers with a score of 0.5–1.0.

<sup>1</sup> The strength of therapeutic recommendations is “moderate” for intermediate metabolizers, and “strong” for all other metabolizers.

Table is adapted from Crews K.R. et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy. 2014 update. Clinical pharmacology and therapeutics. 2014;95(4):376–82 (2).

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# Therapeutic recommendations based on Genotype from authoritative sources

## Therapeutic Recommendations Based on Genotype

This section contains excerpted<sup>1</sup> information on gene-based dosing recommendations. Neither other parts of this review contain the complete recommendations from the sources.

**2015 Statement from the US Food and Drug Administration (FDA)** Respiratory depression occurred in children who received codeine in the post-operative period following tonsillectomy and had evidence of being homozygous for the CYP2D6 poor metabolizer phenotype. The same for isozyme variant D6 [CYP2D6] exposed to high levels of morphine.

Some individuals may be ultra-rapid metabolizers as \*1/\*1xN or \*/\*2xN). This is more common in Chinese and Japanese, or North Africans, Ethiopians; codeine into its active metabolite results in higher than expected rapid metabolism may have extreme sleepiness, confusion.

Please review the complete therapeutic recommendations that

**2014 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)** A patient's response to codeine, an analgesic commonly used in pediatric patients, is determined by their CYP2D6 genotype. Patients with intermediate or poor metabolizer phenotypes may require lower doses of codeine, as recommended in the product label, is warranted phenotype (i.e., a CYP2D6 activity score of 1.0–2.0). Likewise, a patient with an intermediate metabolizer phenotype (i.e., activity score of 1.0–2.0) may respond more closely for less-than-optimal response and should be offered an alternative substrate tramadol is selected as alternative therapy in intermediate due to the possibility of poor response.

If clinical genotyping identifies a patient as a CYP2D6 poor metabolizer, the avoidance of codeine and the use of an alternative analgesic other than the CYP2D6 substrates tramadol, hydrocodone, or buprenorphine are preferred. There is insufficient evidence in the literature to recommend especially considering the evidence that select adverse effects do not occur in a patient identified as a CYP2D6 ultrarapid metabolizer (i.e., act should be made to avoid the risk of severe toxicity with a "normal"

Please review the complete therapeutic recommendations that

**2013 Clinical practice Guideline from the "Canadian Pharmacogenomics Network for Drug Safety (CPNDS) Clinical Recommendations Group: CYP2D6 genotyping for safe and efficacious codeine therapy":**

### 1. Who should be tested and when?

- Young children about to receive codeine for pain management and women about to receive codeine for postpartum pain while breastfeeding should be tested for CYP2D6 (Grade A – strong recommendation).
- Children and adults who continue to have pain despite high doses of codeine should be tested for CYP2D6 (Grade B – moderate recommendation).
- Genetic testing for CYP2D6 should be considered before administering codeine for the first time in all children and adults in order to rule out non-responders and to identify individuals who may be susceptible to adverse effects from codeine (Grade C – optional recommendation).

### 2. What gene variants should be tested?

Given the numerous polymorphisms in CYP2D6 and the diversity of the Canadian population, a full-scale analysis of both common and rare CYP2D6 variants is advised (Grade B - moderate recommendation)

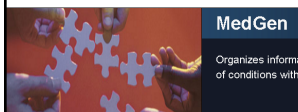
- CYP2D6 alleles with decreased or no function: CYP2D6 \*3, \*12, \*14-13, 17, 19, 20, 29, 40-42, 44, 49, 50, 54, 56, 59, \*4XN, \*10XN
- CYP2D6 alleles with normal or increased function: CYP2D6 \*2 (normal), \*1XN (increased), \*2XN (increased), \*3XN, \*5XN (increased), \*4XN, in addition to CYP2D6 copy number determination.

### Recommendations: Genotype-Specific Treatment Options

- Poor metabolizers of CYP2D6 should not receive codeine for pain relief (Grade A - strong recommendation).
- Ultrarapid metabolizers of CYP2D6 should avoid codeine for pain relief and receive alternative analgesics that do not have potent CYP2D6 metabolites (Grade B - moderate recommendation).
- Certain populations, especially opioid naïve breastfed neonates of mothers with functional CYP2D6 gene duplications taking codeine and young children may be particularly susceptible to codeine-induced central nervous system depression. Breastfeeding mothers and young children who are ultrarapid metabolizers of CYP2D6 should avoid codeine (Grade A – strong recommendation).
- In individuals with IM or EM CYP2D6 genotypes, codeine can be used as per standard of care. Existing evidence suggests that caution is still warranted in CYP2D6 EMs receiving codeine if they are receiving concomitant therapies that increase the potential side effects of codeine.

## How to incorporate NCBI resources in a clinical setting

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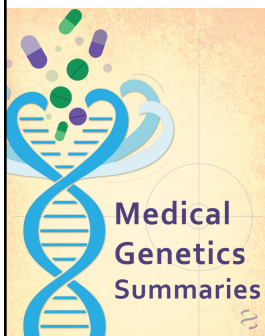
- Consider a differential diagnosis
- Find clinical, molecular & research info on a condition or phenotype
- Use links to relevant information



- Find a suitable test

## How to incorporate NCBI resources in a clinical setting

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- Translate lab report into clinical action:
  - Therapeutic dosing recommendations by phenotype
  - Enzymatic activity status of significant alleles
  - Assignment of likely phenotype based on genotypes
  - Translate variant terms: HGVS, star allele, variant description from the literature, and dbSNP # (rsid)



## MORE INFORMATION

### Medical Genetics Summaries:

➤ <https://www.ncbi.nlm.nih.gov/books/NBK61999/>

### NIH Genetic Testing Registry

➤ <https://www.ncbi.nlm.nih.gov/gtr/>

### MedGen

➤ <https://www.ncbi.nlm.nih.gov/medgen/>

### NCBI Insights Blog:

[ncbiinsights.ncbi.nlm.nih.gov](http://ncbiinsights.ncbi.nlm.nih.gov)



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[info@ncbi.nlm.nih.gov](mailto:info@ncbi.nlm.nih.gov)

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